

THE JOSEPH P. KENNEDY, Jr. LABORATORIES FOR MOLECULAR MEDICINE

Departments of Pediatrics, Genetics, and Obstetrics

Stanford University School of Medicine

Palo Alto

California

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The clinical services of Pediatrics and Obstetrics furnish the immediate background for the research programs relating to mental retardation. They have, of course, the close cooperation of the other clinical departments, especially the Neurology Division and the Department of Psychiatry. Likewise, the work in genetics depends implicitly on the support of Biochemistry. Without these interrelations, we could not possibly function in attempts to further new borderline fields.

The research activities of these departments contain many elements that individually relate to various aspects of mental retardation, and can do so much more effectively by virtue of their coordination within the Kennedy Laboratories. The Laboratories will have an Executive Committee consisting of the respective Department Heads (Drs. Lederberg, Kretchmer, and McLennan) with close support from Drs. Kornberg, Holman, Morrell, and Hamburg (Biochemistry, Medicine, Neurology, and Psychiatry).

The following sheets review the overall research programs of these departments. In addition, please take note of the particular program on Molecular Neurobiology which may represent the most sharply focused convergence of all of these problems. In addition to the research program which centers on molecular neurobiology, we have in mind the development of specific programs in cerebral anoxia (neurology-anesthesia-pediatrics) and in pathology of meiosis (obstetrics-genetics) that might qualify for explicit appointments with Foundation funds. None of us pretends to have a full grasp of the wide range of pertinent disciplines, and we could not hope to undertake such a program without the enthusiastic interest of our colleagues. Thus, Stanford offers a rare opportunity for basic research in mental retardation.

TENTATIVE SPACE AND COSTS BREAKDOWN - BLANK BUILDING
(CLINICAL SCIENCES BUILDING)

Building total will be about 140,000 square feet gross
(plus animal quarters in penthouse)

Estimated total cost at \$40 \$5,600,000 (this is conservative)

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This will be the entire top floor of the Blank Building, and will occupy about 37,000 ft² gross (29,000 ft² net working space). This breaks down to 10,000 ft² for Pediatrics and Genetics, and 4,000 ft² for Obstetrics, plus 5,000 ft² for jointly shared facilities of the three departments, which are, in effect, those which relate most directly to the developmental aspects of medicine.

The pro rata cost of this space would be \$1,480,000 plus additional costs for animal facilities, to about \$1,600,000.

We are asking the Kennedy Foundation to contribute \$1,000,000 to this total.

I had originally mentioned \$2,000,000 which is the amount we would have needed to put the financing of the building over the top. Since then, however, we have had further encouragement for funds for the medical instrumentation laboratories, and have some prospects to make up the remaining gap.

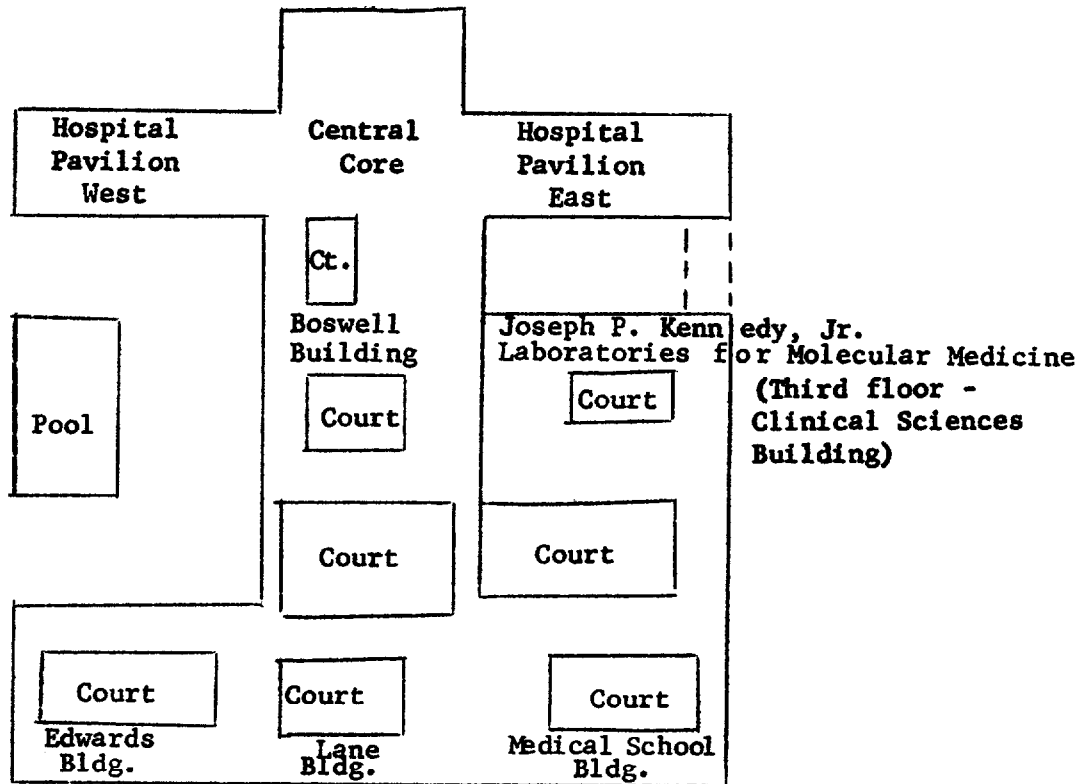
Financing program would be:

Kennedy grant	\$1,000,000
Rockefeller grant	1,000,000
Other private	<u>500,000</u>
	2,500,000
to match a reasonable expectation of N.I.H.	
Health Res. Facility grant	<u>2,000,000</u>
	4,500,000
Medical Instrumentation Laboratory (NASA)	<u>500,000</u>
	5,000,000
Remaining gap	<u>600,000</u>
	\$5,600,000

These costs are for capital construction. We anticipate operating expenses will be relatively easy to manage from other agencies.

ARRANGEMENT OF CLINICAL SCIENCES BUILDING

4 Floors: Gross - 140,000 ft²
Net - 110,000 ft²

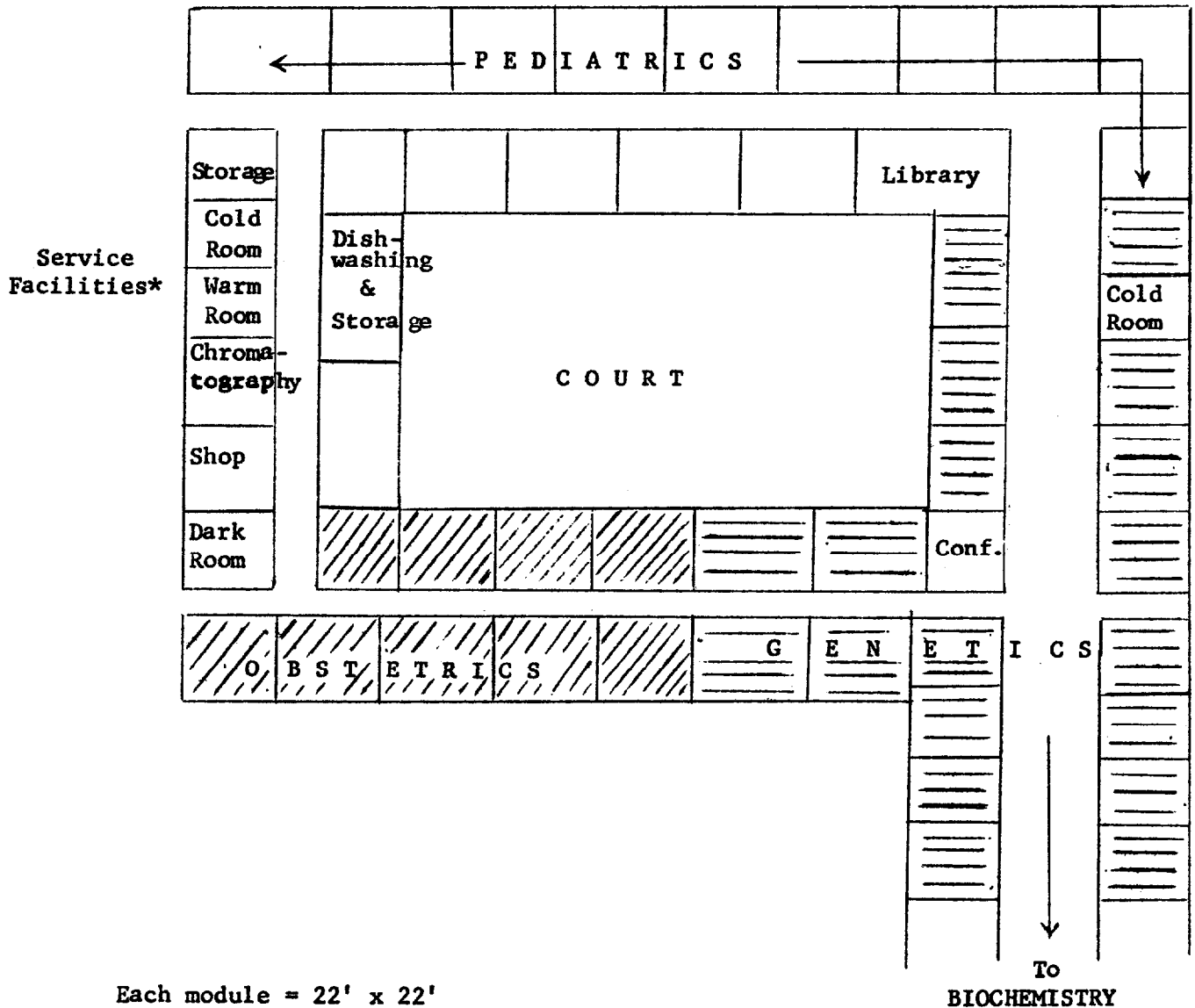


<u>Floors</u>	<u>Allocation</u>
Penthouse	Animal facilities
3	Kennedy Laboratories
	Genetics
	Pediatrics
	Obstetrics
2	Psychiatry
	Surgery
	Basic Medical Sciences
1).	Anesthesia
B)	Medicine - Neurology
	Radiology
	Dermatology
	Medical Instrumentation

CLINICAL SCIENCES BUILDING

Third Floor: Gross - 35,000 ft.
Net - ca 27,000 ft²

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*Includes cold room stock room, dishwashing facilities, chromatography room, etc.

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Research Projects Directly Related to Mental Retardation:

A. Molecular Neurobiology: (Lederberg and Kretchmer)

The transposition of new ideas in molecular biology to problems of the nervous system has been greatly hindered by inadequacy of basic technique and classification of proteins of the central nervous system. We plan a comprehensive laboratory to do this, with a view to testing whether the engram does have a molecular basis, i.e., in the form of a metabolically stable protein which is laid down in connection with the learning process.

As a preliminary speculation to help design experiments, we might ask the question whether the engram is represented by the episequential substitution of glutamin for glutamic acid in the amino acid sequence of an established protein. (Some of the most sophisticated instrumentation of the exobiology program, e.g. an electron-beam scanning mass spectrometer may be invaluable to test some facets of this hypothesis; the cytochemical distribution of N¹⁵ label). We believe a vigorous analytical program could give a new direction to bringing the insights of genetic chemistry into developmental neurology.

B. Prematurity: (Kretchmer, Yaffe, Greenberg, Sunshine)

One of the major concomitants of prematurity is brain damage and subsequent mental retardation. The incidence of prematurity can be decreased by exemplary prenatal care of the mother but those premature infants born must still be cared for with methods which would result in a mentally viable individual. Our studies are directed towards prevention of prematurity, and care of premature infants.

a. Prenatal Care (McLennan, Goodlin, Rantz, and Yaffe)

The Departments of Obstetrics, Medicine, and Pediatrics for the past year have been conducting a joint survey of the incidence of urinary tract infection in pregnant women. Their studies consist of identification of the organism and institution of appropriate therapy, and also investigation of possible routes of infection. Most physicians agree that elimination of urinary tract infection during the prenatal period will have a major effect on incidence of prematurity.

Also, Dr. Goodlin is studying the amniotic fluid and serum of pregnant women who are Rh incompatible to determine extent of anemia in the fetus and consequently obtain factual information regarding the best time for delivery. This information would decrease infant wastage.

b. The Premature Infant (Kretchmer, Yaffe, Greenberg, Sunshine)

These studies are designed to improve techniques of care for premature infants; which could directly effect the incidence of mental retardation. Data indicate that approximately 40 to 50% of babies weighing less than 1500 grams have some neurological deficit. This consequence of prematurity must be related to the delivery as well as physiological handicaps of the infant.

The following table summarizes some of our plans for research on the premature infant:

<u>Department</u>	<u>Investigators</u>	<u>Subject</u>
1. <u>Neurology</u> <u>Pediatrics</u>	Morrell, Frank, Greenberg, Winick, Forrest	Development and evaluation of the central nervous system tested with various stimuli; (sound, light, sensation) and measured electrophysiologically.
2. <u>Pediatrics</u> <u>Anesthesia</u>	Yaffe, Catz, Thomas	Response of infant to administration of sedatives administered to mother.
3. <u>Pediatrics</u>	Robertson, Schafer, Hurwitz	Metabolism of proline and hydroxy-proline--aminoaciduria of the premature infant.
4. <u>Neurology</u> <u>Pediatrics</u>	Morrell Kretchmer Greenberg	Electroencephalographic evidence of passage of amino acids and derivatives across the blood-brain barrier in infants and in older children with phenylketonuria and other metabolic diseases.
5. <u>Pediatrics</u>	Sunshine, Sterk, Doell	Transport of carbohydrates and amino acids across the gastro-intestinal tract.
6. <u>Pediatrics</u> <u>Neurology</u>	Kretchmer Morrell, Frank	The development of periodicity as measured by temperature, hormone production, and cerebral activity.

C. Physiological and Biochemical Handicaps:

a. Neuroembryology - Schafer, Greenberg, Winick

1. Schafer - the mechanisms determining experimental development of anomalies of the central nervous system.
2. Greenberg and Winick - metabolism of catecholamines in the central nervous system and the relationship of development of the autonomic nervous system to morphogenesis.

b. Blood-brain barrier - Yaffe and Catz

Transfer of substances; amino acids, bilirubin, and drugs across the blood-brain barrier. Also, metabolism of bilirubin in relation to kernicterus.

D. Cerebral Anoxia - Thomas, Bunker, Sissman

Includes studies on respiration and circulatory exchange in the newborn. Development of more accurate methods for determination of fetal distress.

E. Metabolic Diseases Associated with Mental Retardation - Greenberg, Kretchmer,

- a. Hypoglycemia - Studies of hypoglycemia in infants particularly as a result of hyperinsulinemia or leucine sensitivity. These entities will be investigated in terms of catecholamine metabolism and eventual development of mental retardation.
- b. Screening of patients with mental retardation for associated metabolic disorders, i.e. aminoacidurias, melliturias.

F. Cytogenetics of Congenital Disease - Luzzatti, Goodlin, Gates

- a. Screening of new cases, furnishes indispensable diagnostic information on the one hand, and on the other uncovers new syndromes based on chromosome imbalance.
- b. Goodlin and others have found that human ova reach the meiotic stage of diakinesis within a few days after birth, and are stored in this stage until ovulation, when the first meiosis occurs. Experimental studies on meiotic pathology are being planned to investigate experimentally the effect of previous exposure to radiation on later non-disjunction, as well as the effect of endocrinological disturbances at the time of ovulation. The first requirement is the development of suitable material to assay such effects in experimental animals, which will probably require direct cytological analysis of young embryos. Concurrently, specimens from human abortions are being studied to determine if any significant fraction, at various stages, are also related to chromosome misfunction.

SUMMARY OF CLINICAL FACILITIES RELATING TO MENTAL RETARDATION

(General services of Pediatrics, Obstetrics, Neurology, and Psychiatry)

Mental Retardation Clinic: Kretchmer, Luzzatti, Winick

Children's Health Council

Premature Infants Ward

Chromosome analysis laboratory: Luzzatti

San Mateo and Santa Clara Counties--Survey of services for the
mentally retarded; case collection: L. C. Waldo

Child Psychiatry: Hamburg, Shirley, Morrell, Pribram

Pediatric Neurology: Iannone, Frank

Specialist appointment pending in Pediatrics

Exceptional Children (Public Schools): H. Jennison

Social work, clinical psychology, general diagnosis services,

Stanford Convalescent Home - provide additional support.

OTHER RESEARCH PROGRAMS IN DEPARTMENTS OF GENETICS, PEDIATRICS, AND OBSTETRICS

The research topics are listed to identify the resources that will support the central work on developmental neurobiochemistry.

A. Genetics:

- | | |
|---|--|
| Lederberg
with several
associates | Genetic chemistry of bacteria
Fractionation of DNA related to specific genes in <u>Bacillus subtilis</u> , and studies on the variation of chemical composition and physical properties of different genes.

Mechanism of entry of DNA into bacteria

Organization of DNA in bacterial nucleus

Replication of DNA

DNA control of specific proteins, especially those related to biosynthesis of aromatic amino acids (cf. phenylketonuria). |
| Herzenberg | Genetics of somatic cells in culture

Immunogenetics of cell surface membranes |
| ----- | Genetics of tissue transplantation (vacant appointment to succeed Nossal partly dependent on space). |
| -----
? Bodmer | Population genetics of man
vacancy: has been filled by visiting appointments from time to time, e.g. L. L. Cavalli-Sforza; will be J. F. Crow in 1963. |
| E. C. Levinthal | Instrumentation for exobiology
Basic methods for characterizing extra-terrestrial life. (This may be indispensable for the cytochemical techniques and the improvement in automated analyses needed for molecular neurobiology program. |

B. Pediatrics:

1. Schwartz and Walters Studies of heme synthesis in various tissues during embryogenesis.
2. Doell, Sunshine,
Sterk and Kretchmer Studies of the developing intestine.
In particular reference to transport of amino acids and disaccharides, and the synthesis of specific disaccharidases.
3. Kretchmer and Brandstr p Metabolism of glycogen in fetal liver, lung and brain; hormonal-enzyme interrelationships.

4. Robertson and Sissman Histochemical and biochemical changes in collagenous connective tissue during development.
5. Yaffe and Catz The relationship of heredity and age to the metabolism of drugs.
6. Tsuboi Studies of nucleotides and phosphate transfer as related to function of cardiac muscle and metabolism of erythrocytes.

C. Obstetrics:

1. Reproductive Physiology - Drs. A. H. Gates, N. Purshottam, S. Purshottam
 Fertilization and transport of the ovum
 Hypothalamic and hypophysial control of oogenesis and ovulation
 Ovular-endometrial requirements for successful nidation
 Sperm migration in the female genital tract--radioactive tagging techniques
 Measurement of gonadotrophic activity by immune mechanisms
2. Reproductive genetics - Dr. A. H. Gates
 Species and strain differences related to nidation efficiency
3. Ovarian-pituitary-adrenocortical interrelationships in amenorrhea, Stein-Leventhal syndrome and other gynecologic endocrinopathies--steroid chemistry, histochemistry, histopathology - Drs. E. C. Sandberg and C. E. McLennan.
4. Human chromosomal genetics - Dr. R. C. Goodlin
 Chromosomal variations during irradiation of gynecological tumors
 Chromosomal patterns in various obstetric and gynecologic disorders
5. Exfoliative cytology - Drs. M. T. and C. E. McLennan
 Cellular responses in disturbed pregnancies
 Cornification indices with recurrent gynecologic neoplasms
 Cellular responses to radiation and chemotherapy

OTHER MEDICAL SCHOOL DEPARTMENTS

Some Projects Relevant to Problem of Mental Retardation

BEHAVIORAL STUDIES

Neurology

Lenore Morrell - Verbal responses in relation to localized cerebral lesions (especially irritative vs. destructive lesions, and compensation to them).

Neurology

Frank Morrell - Diagnosis of specific defects (e.g. auditory vs. visual agnosia) and educational redirection, behavioral disturbances from epileptogenic lesions.

Psychiatry

Karl Pribram - Effect of neurological lesions on pathways of stimulus-processing; techniques for measurement of concept development (problem-solving strategies); development of computer analysis.

Psychiatry

David Hamburg - Influence of manipulation, and interrelation with steroid regulation on development of 'personality' (character of avoidance response).

PHYSIOLOGY: NEURAL AND DEVELOPMENTAL

Neurology

L. Morrell and Koepke - Electrical signs of habituation to constant stimulation (neurological signs of learning).

Neurology

F. Morrell and Chow - Role of synaptic transmission vs. field effects (mass conduction) in learning.

_____ - Cellular mechanisms in epilepsy; mirror field irritation from unilateral lesions.

Pharmacology

K. Killam - Electrophysiological aspects of learning (conditioning to visual stimuli); effects of drugs

Neurology

A. Iannone - Evaluation of cerebral blood flow; the blood-brain barrier.

Neurology

Chow and Morrell - RNA metabolism in epilepsy and stimulation of neurones.

BIOCHEMISTRY

Molecular Biology of Development, Heredity, and Cerebral Function

Department of Biochemistry

Kornberg - replication of DNA; sequence analysis
Josse - episequential alteration of DNA in development
Hogness - DNA-RNA relations
Kaiser - genetic effect of physical alteration of DNA
Lehmann - DNA destroying enzymes
Baldwin - physicochemical studies of DNA
Berg - function of RNA in protein synthesis
Cohn - Immunochemistry; mechanisms of antibody synthesis

Pharmacology

Goldstein - Mutagenic and teratological effects of drugs (esp. caffeine)

Radiology

Kaplan & Kriss - incorporation of base analogues in mammalian DNA
Abrams - radiological diagnosis of congenital disease

Psychiatry

Hamburg - hormonal responses to stress
 biochemical genetics of adrenal metabolism

Instrumentation Laboratory

E. C. Levinthal - (With NASA support, request now being reviewed)

This facility will cooperate with other research activities in the design and construction of novel electronic instrumentation, particularly in fields related to automated biochemical analysis. It will also support work in special purpose computers for use in electrophysiology, radiological picture analysis, and information processing. It will be indispensable for work in cytochemistry and in neurobiochemistry.

A Neurological View of Mental Retardation

(Memorandum by F. Morrell, M. D., Professor of Neurology)

"In view of the fact that lack of intellectual development might quite reasonably be viewed as a disorder of brain function, it is somewhat surprising that so little of the research in this field has been carried out by investigators having a high degree of neurological sophistication. This peculiar circumstance has resulted in clinical classifications of mental retardation which are absurdly over-simplified. Some workers simply divide this large body of patients into those with and without "brain damage". Usually those considered to be "brain damaged" have other abnormalities, such as seizures or permanent physical deficits in addition to an "intellectual" impairment. However, it has been amply demonstrated that neurological lesions may be subclinical with respect to the usual methods of examination and yet nevertheless exert a profound influence on behavior and on particular performance . . .

In my opinion, these considerations are important in any discussion of research in mental retardation for the following reasons: Although there is a crying need for basic biochemical studies of the developing nervous system (and I agree that it is mostly likely that the really fundamental advances will come through such research), there is still a tremendous amount that needs to be done with the patients themselves who suffer from this condition in any of its various forms. In the first place, there needs to be a much more detailed analysis of the intellectual or perceptual deficit itself in each given case. This should be carried out with the use of newer testing methods developed in experimental laboratories where performance and perceptual functions have been rigorously related to site and kind of cerebral lesion . . .

At the present time our laboratories are actively engaged in animal experimentation directed at the problem of discerning disorders in protein metabolism related to epileptiform discharge. The same experimental animals are being used to further define the relationship between such paroxysmal electrical activity and behavioral disturbances. Thus, there is a background of work already in progress which should make it relatively easy to extend these approaches to clinical problems involving mental retardation. However, all of these studies require that an active research program in basic biochemistry and molecular biology be under way at the same time and in the same institution.

I would like only to add that I think the problems posed by the clinical circumstance in which there is lack of intellectual development have very far-reaching and fundamental implications. Neurologists in general have neglected this field, and I would like to emphasize that this particular neurological unit is interested and willing to participate actively in such a program."

Memorandum from David A. Hamburg, M. D., Professor of Psychiatry

"As the Department of Psychiatry develops, considerable research pertinent to mental retardation will be undertaken. The principal research directions of this department will involve inquiry into relations of endocrine function, the central nervous system and behavior. For example, in the area of human biochemical genetics there will be research on metabolism of adrenal hormones as related to brain function and behavioral disturbances.

Another area of investigation pertinent to retardation will be undertaken in the newly established Behavioral Endocrinology Laboratory, headed by Dr. Seymour Levine. This laboratory will be concerned entirely with developmental problems, seeking to analyze experimentally (first in rodents, later in primates) the effects of manipulation of endocrine and environmental variables in early life on learning abilities and endocrine functions of the adult organisms.

In Child Psychiatry, the Department is currently considering an affiliation with the Peninsula Children's Center (a small day-care unit for retarded and autistic children). This affiliation, or some other development of a small inpatient unit for child psychiatry, would permit intensive research on mentally retarded children. The direction of such research would, of course, be determined to a significant extent by subsequent faculty appointments. Our present hope is that such research might pursue two lines of inquiry: (1) possible abnormalities in metabolism of adrenal or thyroid hormones; (2) systematic exploration of latent learning capacities, comparing several approaches that utilize newer information and techniques emerging from recent research on basic learning processes.

The Department of Psychiatry is participating in a strong inter-departmental program of basic research in the brain-and behavior field. The principal concentration of work in this field is on the neural basis of learning, especially as regards forebrain anatomy, electrophysiology, and molecular mechanisms. This work is located in the Departments of Psychiatry, Medicine (Neurology) and Pharmacology; the senior investigators are Doctors Pribram, Morrell, Killam, and Chow.

EDUCATIONAL ACTIVITIES OF THE JOSEPH P. KENNEDY, Jr. LABORATORIES

1. Graduate research training programs in Genetics, Pediatrics, and Neurology under existing and prospective training grants.
2. Fellowships in research laboratories--the most effective method of research training.
3. Seminar on neurobiological approaches to the study of mental retardation (J. Lederberg, Chairman).
4. Clinic conferences on mental retardation (L. Luzzatti).
5. Courses on growth and development--considerable portions are devoted to neural development.
6. Library of the Kennedy Laboratories will be a center for collecting extensive material in the field of mental retardation.
7. The personal interest of so many faculty members in mental retardation will be included in the content of the general medical courses for which they are responsible.
8. Professional publications from these programs will carry the imprint, "Contribution _____ from the Kennedy Laboratories for Molecular Medicine".